# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

**Application Number : 040188**

**Trade Name : CARISOPRODOL TABLETS 350MG**

**Generic Name: Carisoprodol Tablets 350mg USP**

**Sponsor : Amide Pharmaceutical, Inc.**

**Approval Date: March 7, 1997**

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION 040188**

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| | Included | Pending Completion | Not Prepared | Not Required |
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| **Tenative Approval Letter** | | | | |
| **Approvable Letter** | | | | |
| **Final Printed Labeling** | X | | | |
| **Medical Review(s)** | | | | |
| **Chemistry Review(s)** | X | | | |
| **EA/FONSI** | | | | |
| **Pharmacology Review(s)** | | | | |
| **Statistical Review(s)** | | | | |
| **Microbiology Review(s)** | | | | |
| **Clinical Pharmacology Biopharmaceutics Review(s)** | | | | |
| **Bioequivalence Review(s)** | X | | | |
| **Administrative Document(s)** | | | | |
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| | | | | |

# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number 040188**

## APPROVAL LETTER

ANDA 40-188

Amide Pharmaceutical, Inc.
Attention: Jasmine Shah
101 East Main Street
Little Falls, NJ 07424

MARCH 7 1997

Dear Madam:

This is in reference to your abbreviated new drug application dated May 17, 1996 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Carisoprodol Tablets USP, 350 mg.

Reference is also made to your amendments dated October 31, 1996 and February 14, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Carisoprodol Tablets USP, 350 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Soma® Tablets, 350 mg of Wallace Laboratories). Your dissolution testing should be incorporated into the stability and quality control programs using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #40-188
ANDA #40-188/Division file
Field Copy
HFD-600/Reading file
HFD-8/P.Savino
HFD-610/J.Phillips
HFD-82

Endorsements:

HFD-625/SBrown/12-11-96
HFD-613/CHolquist/12-12-96
HFD-613/C.Hoppes for J.Grace/12-13-96
HFD-625/MSmela/12-12-96
HFD-617/SO'Keefe, PM/12-23-96
X:\new\firmsam\amide\ltrs&rev\40188.apl
FT by MM December 24, 1996
Approval Letter

# CENTER FOR DRUG EVALUATION AND RESEARCH

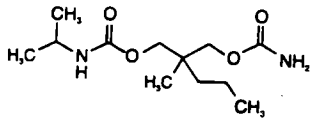
## APPLICATION NUMBER 040188

## FINAL PRINTED LABELING

# CARISOPRODOL TABLETS, USP 350 mg

## DESCRIPTION:

Carisoprodol is a white, crystalline powder, having a mild, characteristic odor and a bitter taste. Carisoprodol is N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate and its molecular weight is 260.34. Its structural formula is as follows:



Each tablet for oral administration contains 350 mg carisoprodol. In addition, each tablet contains the following inactive ingredients: hydroxypropyl methyl cellulose, lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, stearic acid and talc.

## CLINICAL PHARMACOLOGY:

Carisoprodol produces muscle relaxation in animals by blocking interneuronal activity in the descending reticular formation and spinal cord. The onset of action is rapid and effects last four to six hours.

## INDICATIONS AND USAGE:

Carisoprodol is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Carisoprodol does not directly relax tense skeletal muscles in man.

## CONTRAINDICATIONS:

Acute intermittent porphyria as well as allergic or idiosyncratic reactions to carisoprodol or related compounds such as meprobamate, mebutamate, or tybamate.

## WARNINGS:

**Idiosyncratic Reactions:** On very rare occasions, the first dose of carisoprodol has been followed by idiosyncratic symptoms appearing within minutes or hours. Symptoms reported include: extreme weakness, transient quadriplegia, dizziness, ataxia, temporary loss of vision, diplopia, mydriasis, dysarthria, agitation, euphoria, confusion, and disorientation. Symptoms usually subside over the course of the next several hours. Supportive and symptomatic therapy, including hospitalization, may be necessary.

**Usage in Pregnancy and Lactation:** Safe usage of this drug in pregnancy or lactation has not been established. Therefore, use of this drug in pregnancy, in nursing mothers, or in women of childbearing potential requires that the potential benefits of the drug be weighed against the potential hazards to mother and child. Carisoprodol is present in breast milk of lactating mothers at concentrations two to four times that of maternal plasma. This factor should be taken into account when use of the drug is contemplated in breast-feeding patients.

**Usage in children:** Because of limited clinical experience, Carisoprodol is not recommended for use in patients under 12 years of age.

**Potentially Hazardous Tasks:** Patients should be warned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a motor vehicle or operating machinery.

**Additive Effects:** Since the effects of carisoprodol and alcohol or carisoprodol and other CNS depressants or psychotropic drugs may be additive, appropriate caution should be exercised with patients who take more than one of these agents simultaneously.

**Drug Dependence:** In dogs, no withdrawal symptoms occurred after abrupt cessation of carisoprodol from doses as high as 1 gm/kg/day. In a study in man, abrupt cessation of 100 mg/kg/day (about five times the recommended daily adult dosage) was

followed in some subjects by mild withdrawal symptoms such as abdominal cramps, insomnia, chilliness, headache, and nausea. Delirium and convulsions did not occur. In clinical use, psychological dependence and abuse have been rare, and there have been no reports of significant abstinence signs. Nevertheless, the drug should be used with caution in addiction-prone individuals.

**Precautions:** Carisoprodol is metabolized in the liver and excreted by the kidney; to avoid its excess accumulation, caution should be exercised in administration to patients with compromised liver or kidney function.

## ADVERSE REACTIONS:

**Central Nervous System** - Drowsiness and other CNS effects may require dosage reduction. Also observed: dizziness, vertigo, ataxia, tremor, agitation, irritability, headache, depressive reactions, syncope, and insomnia. (See also Idiosyncratic Reactions under "Warnings").

**Allergic or Idiosyncratic** - Allergic or idiosyncratic reactions occasionally develop. They are usually seen within the period of the first to fourth dose in patients having had no previous contact with the drug. Skin rash, erythema multiforme, pruritus, eosinophilia, and fixed drug eruption with cross reaction to meprobamate have been reported with carisoprodol. Severe reactions have been manifested by asthmatic episodes, fever, weakness, dizziness, angioneurotic edema, smarting eyes, hypotension, and anaphylactoid shock. (See also Idiosyncratic Reactions under "Warnings").
In case of allergic or idiosyncratic reactions to carisoprodol, discontinue the drug and initiate appropriate symptomatic therapy, which may include epinephrine, antihistamines, and in severe cases corticosteroids. In evaluating possible allergic reactions, also consider allergy to excipients (information on excipients is available to physicians on request).

**Cardiovascular** - Tachycardia, postural hypotension, and facial flushing.

**Gastrointestinal** - Nausea, vomiting, hiccup, and epigastric distress.

**Hematologic** - Leukopenia, in which other drugs or viral infection may have been responsible, and pancytopenia, attributed to phenylbutazone, have been reported. No serious blood dyscrasias have been attributed to carisoprodol.

## OVERDOSAGE:

Overdosage of carisoprodol has produced stupor, coma, shock, respiratory depression, and, very rarely, death. The effects of an overdosage of carisoprodol and alcohol or other CNS depressants or psychotropic agents can be additive even when one of the drugs has been taken in the usual recommended dosage. Any drug remaining in the stomach should be removed and symptomatic therapy given. Should respiration or blood pressure become compromised, respiratory assistance, central nervous system stimulants, and pressor agents should be administered cautiously as indicated. Carisoprodol is metabolized in the liver and excreted by the kidney. Although carisoprodol overdosage experience is limited, the following types of treatment have been used successfully with the related drug meprobamate: diuresis, osmotic (mannitol) diuresis, peritoneal dialysis, and hemodialysis (carisoprodol is dialyzable). Careful monitoring of urinary output is necessary and caution should be taken to avoid overhydration. Observe for possible relapse due to incomplete gastric emptying and delayed absorption. Carisoprodol can be measured in biological fluids by gas chromatography (Douglas, J.F. et al: *J Pharm Sci* 58: 145, 1969)

## DOSAGE AND ADMINISTRATION:

The usual adult dosage of carisoprodol tablets is one 350 mg tablet, three times daily and at bedtime. Usage in patients under 12 is not recommended.

## HOW SUPPLIED:

Carisoprodol Tablets, USP 350 mg: White, round, unscored tablets, debossed with A136 on one side, are available in bottles of 100 (NDC 52152-136-02) and 1000 (NDC 52152-136-05).

Store at controlled room temperature 15° - 30°C (59° - 86°F).

Dispense in a tight, light-resistant container as defined in the USP.

MANUFACTURED BY:
AMIDE PHARMACEUTICAL, INC.
LITTLE FALLS, NJ 07424

7850-00 10/96

Mango

AMIDE

NDC 52152-136-02

# CARISOPRODOL TABLETS, USP 350 mg

**CAUTION:** Federal law prohibits dispensing without prescription.

100 TABLETS

**Each Tablet Contains:**
Carisoprodol ..... 350 mg

**USUAL DOSAGE:** Adults: One tablet three times daily and at bedtime.

See accompanying literature for full prescribing information.

Dispense in a tight, light-resistant container as defined in the USP.

Store at controlled room temperature 15°-30°C (59°-86°F).

**KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.**

7799-00

N 3 52152-136-02 2

Control No.:

Exp. Date:

**AMIDE PHARMACEUTICAL, INC.** 101 EAST MAIN STREET, LITTLE FALLS, N.J. 07424


AMIDE

NDC 52152-136-02

CARISOPRODOL TABLETS, USP 350 mg

CAUTION: Federal law prohibits dispensing without prescription.

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KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

7799-00

N 3 52152-136-02 2

Control No.:

Exp. Date:

AMIDE PHARMACEUTICAL, INC. 101 EAST MAIN STREET, LITTLE FALLS, N.J. 07424



AMIDE

NDC 52152-136-02

CARISOPRODOL TABLETS, USP 350 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

Each Tablet Contains:
Carisoprodol ..... 350 mg

USUAL DOSAGE: Adults: One tablet three times daily and at bedtime.

See accompanying literature for full prescribing information.

Dispense in a tight, light-resistant container as defined in the USP.

Store at controlled room temperature 15°-30°C (59°-86°F).

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

7799-00

N 3 52152-136-02 2

Control No.:

Exp. Date:

AMIDE PHARMACEUTICAL, INC. 101 EAST MAIN STREET, LITTLE FALLS, N.J. 07424

AMIDE

NDC 52152-136-05

# CARISOPRODOL TABLETS, USP 350 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

7 1997

N 3 52152-136-05 3

**Each Tablet Contains:**
Carisoprodol ..... 350 mg
**USUAL DOSAGE:** Adults: One tablet three times daily and at bedtime.
See accompanying literature for full prescribing information.
This is a bulk container. Not intended for household use.
Dispense in a tight, light-resistant container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
**KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.**

7800-00

Control No.:
Exp. Date:

**AMIDE PHARMACEUTICAL, INC.** 101 EAST MAIN STREET, LITTLE FALLS, N.J. 07424

AMIDE

NDC 52152-136-05

CARISOPRODOL TABLETS, USP 350 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

7 1997

N 3 52152-136-05 3

Each Tablet Contains:
Carisoprodol ..... 350 mg
USUAL DOSAGE: Adults: One tablet three times daily and at bedtime.
See accompanying literature for full prescribing information.
This is a bulk container. Not intended for household use.
Dispense in a tight, light-resistant container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

7800-00

Control No.:
Exp. Date:

AMIDE

NDC 52152-136-05

CARISOPRODOL TABLETS, USP 350 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

7 1997

N 3 52152-136-05 3

Each Tablet Contains:
Carisoprodol ..... 350 mg
USUAL DOSAGE: Adults: One tablet three times daily and at bedtime.
See accompanying literature for full prescribing information.
This is a bulk container. Not intended for household use.
Dispense in a tight, light-resistant container as defined in the USP.
Store at controlled room temperature 15°-30°C (59°-86°F).
KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

7800-00

Control No.:
Exp. Date:

AMIDE PHARMACEUTICAL, INC. 101 EAST MAIN STREET, LITTLE FALLS, N.J. 07424

**APPLICATION NUMBER 040188**

# CHEMISTRY REVIEW(S)

[redacted] NUMBER 40-188

**FIRM:** Amide Pharmaceutical, Inc. **DOSAGE FORM:** Tablet

**STRENGTH:** 350 mg

**DRUG:** Carisoprodol

**CGMP STATEMENT/EIR UPDATE STATUS:** EER dated 7/22/96 is pending.

**BIO STUDY:** Review stamp dated 12/5/96.

The waiver of *in vivo* bioequivalence study requirements was granted.

**METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):**

N/A Drug product is listed in USP 23.

**STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?** Yes

Data are satisfactory to support a tentative 24 month expiry date.

**LABELING:**

Satisfactory. Review dated 11/13/96.

**STERILIZATION VALIDATION (IF APPLICABLE):**

N/A

**SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):**

#5415A -

yield -

Active ingredient by is acceptable.

**SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA SAME PROCESS):**

Same batch.

**PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?** Yes

Proposed production batch sizes - tablets
tablets
tablets

Review Chemist: Shirley S. Brown
Supervisor: Michael Smela
Date: December 11, 1996

12/11/96

12/12/96

1. CHEMISTRY REVIEW NO. 2

2. ANDA #40-188

3. NAME AND ADDRESS OF APPLICANT

Amide Pharmaceutical, Inc.
101 East Main Street
Little Falls, NJ 07424

4. BASIS OF SUBMISSION

Accepted by OGD

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME

Carisoprodol

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

5/17/96 - original submission
7/1/96 - FDA letter requesting additional information
7/9/96 - amendment responding to FDA's letter of 7/1/96
7/16/96 - amendment (completed form FDA 356h)
10/3/96 - NAL for chem review #1
*10/31/96 - amendment responding to FDA's letter of 10/3/96

10. PHARMACOLOGICAL CATEGORY

Skeletal Muscle Relaxant

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM

tablet

14. POTENCY

350 mg

15. CHEMICAL NAME AND STRUCTURE

See review #1.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

N/A

18. CONCLUSIONS AND RECOMMENDATIONS

A. Chemistry issues are closed.

B. Review of labeling per the 10/31/96 amendment is pending.

C. A waiver of in vivo bioequivalence study per 21 CFR 320.22(b)(1) for the drug product is requested. The waiver is pending, and the decision to grant or not grant the waiver will be made by Division of Bioequivalence.

D. EER - Pending. The Office of Compliance will decide cGMP Compliance Status of facilities involved in the manufacture/testing of the subject drug product and the active ingredient.

19. REVIEWER: DATE COMPLETED:

Shirley S. Brown November 8, 1996

cc: ANDA #40-188
ANDA #40-188/Division File
Field Copy

Endorsements:

HFD-625/SBrown/11/8/96
HFD-625/MSmela/11-12-96
x:\new\firmsam\amide\ltrs&rev\40188.r#2
F/T by MM November 13, 1996

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 040188

## BIOEQUIVALENCE REVIEW(S)

ANDA 40-188

Amide Pharmaceuticals, Inc.
Attention: Jasmine Shah, M.S., R.Ph.
101 E. Main Street
Little Falls NJ 07424

DEC 10 1996

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Carisoprodol Tablets USP, 350 mg

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DEC 5 1996

**Carisoprodol Tablets, USP**
**350 mg**
**ANDA # 40-188**
**Reviewer: Man M. Kochhar**
**40188DW.796**

**Amide Pharmaceutical, Inc.**
**Little Falls, NJ**
**Submission Date:**
**July 16, 1996**

## REVIEW OF DISSOLUTION DATA AND A WAIVER REQUEST

Amide Pharmaceutical has submitted dissolution data on its product carisoprodol tablets, USP 350 mg comparing it to the reference product Soma tablets, 350 mg manufactured by Wallace, in support for a waiver request for the bioequivalence study requirements. Carisoprodol produces muscle relaxation and is indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions. The usual adult dose is one 350 mg tablet, 3 times a day and at bed time.

**Comments:**

1. Carisoprodol Tablets, USP 350 mg, is AA rated.

2. The test product does not contain any inactive ingredients that may cause a bioequivalence problem. The reference product contains the following inactive ingredients: alginic acid, magnesium stearate, potassium sorbate, starch, and tribasic calcium phosphate. The formulation of the test product is as follows:

### Formulation of the Test Product

Each Tablet Contains:

| | |
|---|---|
| Carisoprodol, USP | 350.0 mg |
| Lactose Monohydrate, NF | |
| Sodium Starch Glycolate, NF | |
| Hydroxypropylmethyl Cellulose 2910, USP | |
| Microcrystalline Cellulose, (101), NF | |
| Stearic Acid, NF | |
| Talc, USP | |
| Purified Water, USP | |
| TOTAL | 525.0 mg |

Batch Size:

3. The comparative dissolution data on the test and reference products meet the USP dissolution specifications. The results are shown in Table 1.

4. The waiver of in vivo bioequivalence requirements is granted.

## TABLE 1

### In Vitro Dissolution Testing

Drug: Carisoprodol Tablets, USP
Strength: 350 mg
ANDA # 40-188
Firm: Amide Pharmaceutical
Submission Date: July 16, 1996

**Conditions for Dissolution Testing:**

USP XXIII Apparatus 2 (paddle) at 75 rpm
No. of Units: 12
Medium: 0.05 M Phosphate Buffer, pH 6.9
Volume: 900 mL
Specifications: NLT . in 60 minutes
Reference Drug: Soma
Assay Methodology·

**Results:**

| Times in Minutes | Test Product Lot # 5415A Strength 350 mg | | | Reference Product Lot # 4J1037A Strength 350 mg | | |
|---|---|---|---|---|---|---|
| | Mean | Range | St Dev | Mean | Range | St Dev |
| 30 | 93 | | 0.5 | 79 | | 1.0 |
| 45 | 95 | | 0.5 | 84 | | 0.8 |
| 60 | 97 | | 0.5 | 89 | | 1.8 |

**Recommendations:**

1. The dissolution testing conducted by Amide Pharmaceutical on its Carisoprodol 350 mg tablets, lot # 5415 A is acceptable.

2. The Division of Bioequivalence agrees that the information submitted by Amide Pharmaceutical demonstrates that its Carisoprodol tablets, USP, 350 mg, falls under 21 CFR 320.22 (d)(2) of the Bioavailability/Bioequivalence Regulations. The waiver of an in vivo bioequivalence study for the test product is granted. The test product is deemed bioequivalent to Wallace's Soma tablets, 350 mg.

3. The dissolution testing should be incorporated into thr firm's manufacturing controls and stability program. The dissolution testing should be conducted in the 900 mL of 0.05 M phosphate buffer (pH 6.9) at 37° C using USP XXIII apparatus 2 (paddle) at 75 rpm. The test product should meet the following specifications:

> Not less tha· of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

The firm should be informed of the recommendations.

Man M. Kochhar, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE _____ Date: 11/14/96
Ramakant M. Mhatre, Ph.D.
Chief, Branch III
Division of Bioequivalence

Concur: _____ Date: 12/5/96
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

MMKochhar/mmk/10-1-96, 11-14-96; 40-188

cc: ANDA # 40-188 original, HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Kochhar), Drug File, Division File